

Appl. No. : 09/853,080  
Filed : May 9, 2001

possibly deleted from one or two amino acids of the terminal dipeptide Ser-Leu or one or more amino acids of the tetrapeptide Val-Lys-Ser-Leu (SEQ ID NO: 47)

- the epitope glycine 2242 to leucine 2251 inclusive, defined by the following sequence:

SEQ ID NO.:29:

Gly Val Thr Thr Gln Gly Val Lys Ser Leu

possibly deleted from one or two amino acids of the terminal dipeptide Ser-Leu, said epitope presenting a possible partial overlapping with a known monoclonal antibody binding site ESH8 2248-2285

- the epitope isoleucine 2262 to glutamine 2270 inclusive, defined by the following sequence:

SEQ ID NO.:30:

Ile Ser Ser Ser Gln Asp Gly His Gln

the epitope leucine 2273 to serine 2289 inclusive, defined by the following sequence (P14):

SEQ ID NO.:31:

Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp  
Ser

- the epitope proline 2292 to tyrosine 2305 inclusive, defined by the following sequence (P15):

SEQ ID NO.:32:

Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr

possibly deleted from one or more amino acids of the terminal tripeptide Thr-Arg-Tyr (SEQ ID NO: 48) involved in the phospholipid von Willebrand factor binding site

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**IN THE SEQUENCE LISTING:**

**Please replace the Sequence Listing with the accompanying Substitute Sequence Listing, immediately following the "VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

**REMARKS**

The following remarks address the Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures:

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### **I. Amendments to the Specification**

The specification has been amended to incorporate sequence identification numbers for amino acid sequences described in the specification as filed containing three or more amino acids. The specification has also been amended to correct hard returns in the middle of some of the sequences provided therein. As a result, the Sequence Listing has been replaced with the accompanying Sequence Listing to reflect these additional sequences. Support for these additional sequences is found in the sequences within the specification as filed beginning on page 7, at line 24 through page 13, line 19, and again on page 17, at line 25 through page 28, line 28. Thus, no new matter has been added herewith.

These changes made to the specification by the current amendment, including insertions and [deletions], are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment. No new matter has been added herewith.

### **II. Sequence Submission Statement**

I hereby state that the amendments, made in accordance with 37 C.F.R. §1.825(a), included in the substitute Sequence Listing submitted herewith are supported in the application, as filed, at page 7, line 24 to page 13, line 19 and at page 17, line 25 to page 23, line 28. I hereby state that the substitute Sequence Listing does not include new matter.

I hereby state that the substitute copy of the computer readable form, submitted in accordance with 37 C.F.R. §1.825(b), is the same as the paper copy of the Substitute Sequence Listing provided herewith.

### **III. Conclusion**

Applicants have amended the Sequence Listing to include sequences previously without sequence identification numbers in the specification as filed. As a result, Applicants have submitted herewith a substitute Sequence Listing in paper and the identical listing in computer readable form. In addition, sequence identification numbers have been incorporated into the specification for the additional sequences within the substitute Sequence Listing.

In view of the foregoing, Applicants respectfully submit the present application is in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

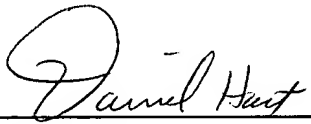
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Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Oct. 30, 2002

By:   
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

The paragraphs beginning at line 22 on page 7 and ending at line 19 on page 13 have been amended as follows:

SEQ ID NO:1:

Arg Asp Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr ,  
possibly deleted from one or more amino acids of the tetrapeptide Arg-Asp-Ile-Thr (SEQ ID NO: 34) or one or two of the last amino acids of the peptide Asp-Tyr,  
the epitope aspartic acid 1681 to arginine 1696 inclusive, defined by the following sequence:

SEQ ID NO:2:

Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg ,  
possibly deleted from one or more amino acids of the epitope Asp-Glu-Asp-Glu (SEQ ID NO: 35),

the epitope threonine 1739 to tyrosine 1748 inclusive, defined by the following sequence:

SEQ ID NO:3:

Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr ,  
the epitope asparagine 1777 to phenylalanine 1785 inclusive, defined by the following sequence:

SEQ ID NO:4:

Asn Gln Ala Ser Arg Pro Tyr Ser Phe ,  
possibly deleted from one or two amino acids of the terminal dipeptide Ser-Phe or the tetrapeptide Pro-Tyr-Ser-Phe (SEQ ID NO: 36),

the epitope glutamic acid 1794 to tyrosine 1815 inclusive, defined by the following sequence:

SEQ ID NO:5:

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr ,  
possibly deleted from one or more amino acids from the first tripeptide Glu-Asp-Gln (SEQ ID NO: 37) or the first nonapeptide Glu-Asp-Gln-Arg-Gln-Gly-Ala-Glu-Pro (SEQ ID NO: 38),

the epitope methionine 1823 to aspartic acid 1831, defined by the following sequence:

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SEQ ID NO:6:

Met Ala Pro Thr Lys Asp Glu Phe Asp ,

the epitope glutamic acid 1885 to phenylalanine 1891 inclusive, defined by the following sequence:

SEQ ID NO:7:

Glu Thr Lys Ser Trp Tyr Phe ,

the epitope glutamic acid 1885 to alanine 1901 inclusive, defined by the following sequence:

SEQ ID NO:8:

Glu Thr Lys Ser Trp Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala ,

possibly deleted from one or more amino acids from the heptapeptide Gly-Thr-Lys-Ser-Trp-Phe-Thr (SEQ ID NO: 39) or from the tripeptide Cys-Arg-Ala (SEQ ID NO: 40),

the epitope aspartic acid 1909 to arginine 1917 inclusive, defined by the following sequence:

SEQ ID NO:9:

Asp Pro Thr Phe Lys Glu Asn Tyr Arg ,

and the epitope comprised between serine 2018 and histidine 2031 inclusive, defined by the following sequence:

SEQ ID NO:10:

Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His .———

Paragraph 8: An antigenic fragment of the polypeptide sequence A1 according to paragraph 5, which is alanine 108 to methionine 355 inclusive, preferably alanine 108 to alanine 227 inclusive.

Paragraph 9: A sequence epitope of the fragment according to paragraph 8, which is selected from the group consisting of:

the epitope alanine 108 to valine 128 inclusive, defined by the following sequence:

SEQ ID NO:11:

Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val ,

possibly deleted from the terminal amino acids alanine and/or valine,  
the epitope glutamic acid 181 to leucine 192 inclusive, defined by the following sequence:

SEQ ID NO:12:

possibly deleted from one or two amino acids of the terminal dipeptide Thr-Leu,

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the epitope aspartic acid 203 to alanine 227 inclusive, defined by the following sequence:

SEQ ID NO:13:

Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala  
Ser —————Ala Arg Ala,

possibly deleted from one or more amino acids of the nonapeptide Asp-Arg-Asp-Ala-Ala-Ser-Ala-Arg-Ala (SEQ ID NO: 41),

and the epitope aspartic acid 327 to methionine 355 inclusive, defined by the following sequence:

SEQ ID NO:14:

Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr  
Asp Asp ———Asp Leu Thr Asp Ser Glu Met ,

possibly deleted from one or more amino acids of the dipeptide Asp-Ser or the octapeptide Asp-Asp-Leu-Thr-Asp-Ser-Glu-Met (SEQ ID NO: 42),

Paragraph 10: An antigenic fragment of the antigenic polypeptide sequence A2 according to paragraph 5, which is aspartic acid 403 to aspartic acid 725 inclusive, preferably histidine 693 to aspartic acid 725 inclusive.

Paragraph 11: A sequence epitope of the fragment according to paragraph 10, which is selected from the group consisting of:

the epitope aspartic acid 403 to lysine 425 inclusive, defined by the following sequence:

SEQ ID NO:15:

Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys  
Tyr Lys Lys ,

possibly deleted from one or more amino acids of the tetrapeptide Asp-Asp-Arg-Ser (SEQ ID NO: 43),

the epitope valine 517 to arginine 527 inclusive, defined by the following sequence:

SEQ ID NO:16:

Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg ,

possibly deleted from one or the two amino acids of the dipeptide Pro-Arg,

the epitope tyrosine 555 to glutamine 565 inclusive defined by the following sequence:

SEQ ID NO:17:

Tyr Lys Glu Ser Val Asp Gly Arg Gly Asn Gln ,

the epitope histidine 693 to glycine 701 inclusive, defined by the following sequence:

SEQ ID NO:18

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His Asn Ser Asp Phe Arg Asn Arg Gly ,

the epitope serine 710 to aspartic acid 725 inclusive, defined by the following sequence:

SEQ ID NO:19

Ser Cys Asp Lys Asn Thr Gly Asp Tyr Try Gly Asp Ser Tyr Glu Asp ,

the epitope leucine 730 to serine 741 inclusive, defined by the following sequence:

SEQ ID NO:20:

Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser ,

possibly deleted from the terminal amino acid serine and/or the first amino acid leucine,  
the epitope serine 817 to serine 830 inclusive, defined by the following sequence:

SEQ ID NO:21:

Ser Asp Asp Pro Ser Gly Ala Ile Asp Ser Asn Asn Ser .

Paragraph 12: An antigenic fragment of the antigenic polypeptide sequence C according to paragraph 5, which is lysine 2085 to isoleucine 2251 inclusive, or leucine 2273 to tyrosine 2332 inclusive, preferably lysine 2085 to glycine 2121 inclusive or serine 2182 to leucine 2251 inclusive.

Paragraph 13: A sequence epitope of the fragment according to paragraph 12, which is selected from the group consisting of:

the epitope isoleucine 2081 to serine 2095 inclusive, defined by the following sequence

SEQ ID NO:22:

Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser ,

possibly deleted from one or more amino acids of the tetrapeptide Ile-His-Gly-Ile (SEQ ID NO: 44),

the epitope tyrosine 2105 to glycine 2121 inclusive, defined by the following sequence:

SEQ ID NO:23:

Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly ,

possibly deleted from one or more amino acids of the tripeptide Tyr-Ser-Leu (SEQ ID NO: 45),

the epitope asparagine acid 2128 to asparagine acid 2138 inclusive, defined by the following sequence:

SEQ ID NO:24:

Asn Val Asp Ser Ser Gly Ile Lys His Asn ,

the epitope histidine 2152 to arginine 2163 inclusive, defined by the following sequence:

SEQ ID NO:25:

His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg ,

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the epitope serine 2181 to asparagine acid 2198 inclusive, defined by the following sequence:

SEQ ID NO:26:

Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn ,  
possibly deleted from one or more amino acids of the first dipeptide Ser-Tyr or one or more amino acids from the terminal tripeptide Phe-Thr-Asn (SEQ ID NO: 46),

the epitope serine 2204 to glutamine 2222 inclusive, defined by the following sequence:

SEQ ID NO:27:

Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln,

the epitope glutamine 2235 to leucine 2251 inclusive, defined by the following sequence:

SEQ ID NO:28:

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu ,

possibly deleted from one or two amino acids of the terminal dipeptide Ser-Leu or one or more amino acids of the tetrapeptide Val-Lys-Ser-Leu (SEQ ID NO: 47),

the epitope glycine 2242 to leucine 2251 inclusive, defined by the following sequence:

SEQ ID NO:29:

Gly Val Thr Thr Gln Gly Val Lys Ser Leu ,

possibly deleted from one or two amino acids of the terminal dipeptide Ser-Leu,  
the epitope isoleucine 2262 to glutamine 2270 inclusive, defined by the following sequence:

SEQ ID NO:30:

Ile Ser Ser Ser Gln Asp Gly His Gln ,

the epitope leucine 2273 to serine 2289 inclusive, defined by the following sequence:

SEQ ID NO:31:

Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser ,

the epitope proline 2292 to tyrosine 2305 inclusive, defined by the following sequence:

SEQ ID NO:32:

Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr ,

possibly deleted from one or more amino acids of the terminal tripeptide Thr-Arg-Tyr  
(SEQ ID NO: 48),

**The paragraphs beginning at line 25 on page 17 and ending at line 28 on page 23 have been amended as follows:**

SEQ ID NO.:1:

Arg Asp Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr ,



- and possibly deleted from one or more amino acids of the tetrapeptide Arg-Asp-Ile-Thr (SEQ ID NO: 34) (P7), or one or two of the last amino acids of the dipeptide Asp-Tyr
- the epitope aspartic acid 1681 to arginine 1696 (P8) inclusive, defined by the following sequence:  
SEQ ID NO.:2:  
Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg  
possibly deleted from one or more amino acids of the epitope Asp-Glu-Asp-Glu (SEQ ID NO: 35),
  - the epitope threonine 1739 to tyrosine 1748 inclusive, defined by the following sequence:  
SEQ ID NO.:3:  
Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr
  - the epitope asparagine 1777 to phenylalanine 1785 inclusive, defined by the following sequence:  
SEQ ID NO.:4:  
Asn Gln Ala Ser Arg Pro Tyr Ser Phe  
possibly deleted from one or more amino acids of the terminal dipeptide Ser-Phe or tetrapeptide Pro-Tyr-Ser-Phe (SEQ ID NO: 36),
  - the epitope glutamic acid 1794 to tyrosine 1815 inclusive, defined by the following sequence:  
SEQ ID NO.:5:  
Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys Pro  
Asn Glu Thr Lys Thr Tyr ,  
possibly deleted from one or more amino acids of the first tripeptide Glu-Asp-Gln (SEQ ID NO: 37) (P9)) or the first nonapeptide Glu-Asp-Gln-Arg-Gln-Gly-Ala-Glu-Pro (SEQ ID NO: 38),
  - the epitope methionine 1823 to aspartic acid 1831 inclusive, defined by the following sequence:  
SEQ ID NO.:6:  
Met Ala Pro Thr Lys Asp Glu Phe Asp
  - the epitope glutamic acid 1885 to phenylalanine 1891 inclusive, defined by the following sequence:  
SEQ ID NO.:7:  
Glu Thr Lys Ser Trp Tyr Phe
  - the epitope glutamic acid 1885 to alanine 1901 inclusive, defined by the following sequence:

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SEQ ID NO.:8:

Glu Thr Lys Ser Trp Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala

possibly deleted from one or more amino acids from the heptapeptide Glu-Thr-Lys-Ser-Trp-Phe-Thr (SEQ ID NO: 39) or from the tripeptide Cys-Arg-Ala (SEQ ID NO: 40).

- the epitope aspartic acid 1909 to arginine 1917 inclusive, defined by the following sequence:

SEQ ID NO.:9:

Asp Pro Thr Phe Lys Glu Asn Tyr Arg

- the epitope comprised between serine 2018 and histidine 2031 inclusive, defined by the following sequence:

SEQ ID NO.:10:

Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His

Advantageously, the said sequences, specific fragments and epitopes exhibit an antigenic characteristic which is illustrated by Table 1.

Another preferred embodiment of the invention relates to antigenic polypeptide sequence A1 of factor VIII, fragments and/or epitopes of this sequence.

Preferably, the fragments of the said sequence are alanine 108 to methionine 355 inclusive, preferably alanine 108 to alanine 227 inclusive.

The invention also relates to the sequence epitopes of these fragments, in particular:

- the epitope alanine 108 to valine 128 inclusive, defined by the following sequence:

SEQ ID NO.:11:

Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys

Glu Asp Asp Lys Val

possibly deleted from the terminal amino acids alanine and valine (P1)

- the epitope glutamic acid 181 to leucine 192 inclusive, defined by the following sequence:

SEQ ID NO.:12:

Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu

possibly deleted from one or two amino acids of the terminal dipeptide Thr-Leu

- the epitope aspartic acid 203 to alanine 227 inclusive, defined by the following sequence:

SEQ ID NO.:13:

Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln

Asp Arg Asp Ala Ala Ser Ala Arg Ala

possibly deleted from one or more amino acids of the nonapeptide Asp-Arg-Asp-Ala-Ala-Ser-Ala-Arg-Ala (SEQ ID NO: 41)

- the epitope aspartic acid 327 to methionine 355 inclusive, defined by the following sequence:

SEQ ID NO.:14:

Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu

Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met

possibly deleted from one or more amino acids from the terminal dipeptide Asp-Ser or the octapeptide Asp-Asp-Leu-Thr-Asp-Ser-Glu-Met (SEQ ID NO: 42 (P2)).

Another preferred embodiment of the invention relates to the antigenic polypeptide sequence A2 of factor VIII, fragments and/or epitopes of this sequence.

Preferably, the fragments of the said sequence are aspartic acid 403 to serine 840 inclusive, preferably histidine 693 to aspartic acid 725 inclusive.

The invention also relates to the sequence epitopes of these fragments, in particular:

- the epitope aspartic acid 403 to lysine 425 inclusive, defined by the following sequence:

SEQ ID NO.:15:

Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg

Ile Gly Arg Lys Tyr Lys Lys

possibly deleted from one or more amino acids of the tetrapeptide Asp-Asp-Arg-Ser (SEQ ID NO: 43 (P3)),

- the epitope valine 517 to arginine 527 inclusive, defined by the following sequence:

SEQ ID NO.:16:

Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg

possibly deleted from one or the two amino acids of the dipeptide Pro-Arg,

- the epitope tyrosine 555 to glutamine 565 inclusive, defined by the following sequence:

SEQ ID NO.:17:

Tyr Lys Glu Ser Val Asp Gly Arg Gly Asn Gln

- the epitope histidine 693 to glycine 701 inclusive, defined by the following sequence:

SEQ ID NO.:18:

His Asn Ser Asp Phe Arg Asn Arg Gly

- the epitope serine 710 to aspartic acid 725 inclusive, defined by the following sequence (P4):

SEQ ID NO.:19:

Ser Cys Asp Lys Asn Thr Gly Asp Tyr Try Gly Asp Ser Tyr Glu Asp

the epitope leucine 730 to serine 741 inclusive, defined by the following sequence (P4):

SEQ ID NO.:20:

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Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser

possibly deleted from the terminal amino acid serine (P4) and/or the first amino acid leucine

- the epitope serine 817 to serine 830 inclusive, defined by the following sequence (P5):  
SEQ ID NO.:21:

Ser Asp Asp Pro Ser Gly Ala Ile Asp Ser Asn Asn Ser

A final preferred embodiment of the invention relates to the antigenic polypeptide sequence C of factor VIII, and fragments and/or epitopes of this sequence. Preferably, the fragments of the said sequence are histidine 2082 to lysine 2251 inclusive or leucine 2273 to tyrosine 2332 inclusive, preferably lysine 2085 to glycine 2121 inclusive and serine 2181 to leucine 2251 inclusive.

The invention also relates to the sequence epitopes of these fragments, in particular:

- the epitope isoleucine 2081 to serine 2095 inclusive, defined by the following sequence:  
SEQ ID NO.:22:

Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser

possibly deleted from one or more amino acids from the tetrapeptide Ile-His-Gly-Ile (SEQ ID NO: 44)

- the epitope tyrosine 2105 to glycine 2121 inclusive, defined by the following sequence:  
SEQ ID NO.:23:

Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr

Gly

possibly deleted from one or more amino acids of the tripeptide Tyr-Ser-Leu (SEQ ID NO: 45 (P10))

- the epitope asparagine 2128 to asparagine 2138 inclusive, defined by the following sequence:

SEQ ID NO.:24:

Asn Val Asp Ser Ser Gly Ile Lys His Asn

the epitope histidine 2152 to arginine 2163 inclusive, defined by the following sequence:

SEQ ID NO.:25:

His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg

the epitope serine 2181 to asparagine 2198 inclusive, defined by the following sequence:

SEQ ID NO.:26:

Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn

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possibly deleted from one or more amino acids from the terminal tripeptide Phe-Thr-Asn  
(SEQ ID NO: 46 (P11))

- the epitope serine 2204 to glutamine 2222 inclusive, defined by the following sequence  
(P12):

SEQ ID NO.:27:

Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp  
Arg Pro Gln

- the epitope glutamine 2235 to leucine 2251 inclusive, defined by the following sequence  
(P13):

SEQ ID NO.:28:

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu

possibly deleted from one or two amino acids of the terminal dipeptide Ser-Leu or one or  
more amino acids of the tetrapeptide Val-Lys-Ser-Leu (SEQ ID NO: 47)

- the epitope glycine 2242 to leucine 2251 inclusive, defined by the following sequence:

SEQ ID NO.:29:

Gly Val Thr Thr Gln Gly Val Lys Ser Leu

possibly deleted from one or two amino acids of the terminal dipeptide Ser-Leu, said  
epitope presenting a possible partial overlapping with a known monoclonal antibody  
binding site ESH8 2248-2285

- the epitope isoleucine 2262 to glutamine 2270 inclusive, defined by the following  
sequence:

SEQ ID NO.:30:

Ile Ser Ser Ser Gln Asp Gly His Gln

the epitope leucine 2273 to serine 2289 inclusive, defined by the following sequence

(P14):

SEQ ID NO.:31:

Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp  
Ser

- the epitope proline 2292 to tyrosine 2305 inclusive, defined by the following sequence  
(P15):

SEQ ID NO.:32:

Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr

possibly deleted from one or more amino acids of the terminal tripeptide Thr-Arg-Tyr (SEQ ID  
NO: 48) involved in the phospholipid von Willebrand factor binding site

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**A substitute Sequence Listing has been added.**